BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PATENT SPECIFICATION

978,855

NO DRAWINGS

978,855

Date of Application and filing Complete Specification: April 12, 1961.

No. 13129/61.

Application made in United States of America (No. 22692) on April 18, 1960.

Complete Specification Published: Dec. 23, 1964.

Index at acceptance:—C2 C(1D, 1J3B, 1J3C2, 1M1A, 1M1B, 1M1C2, 1Q5, 1Q6B1, 1Q7A, 1Q7B, 1Q8A, 1Q8B, 1Q8C, 1Q8D, 1Q9C, 1Q9E, 1Q9F1, 1Q9G, 1Q9K, 1Q9L, 1Q11D, 1Q11E, 1Q11G, 1Q11J, 2C2, 2C6A, 2C6B, 2C6F, 2C7A2, 2D52); A5 E(1A3A1, 1A3B1, 1A4A2, 1A4A3, 1A4A4, 1A4B3, 1A5A, 1A5D, 1A7A, 1A15, 1A16, 1A17, 1A19); C3 P(7D2A1, 7T2D, 7T2X)

International Classification:—C 07 c (A 61 l, C 08 f)

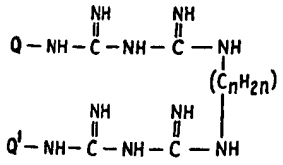
COMPLETE SPECIFICATION

1,1¹-(Alkylene)bis(5-Arylbiguanides), Acid-Addition Salts thereof, and Disinfecting or Sanitizing Compositions containing same

We, STERLING DRUG INC., a corporation organized under the laws of the State of Delaware, United States of America, of 1450 Broadway, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

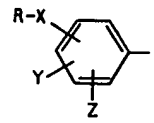
This invention relates to certain novel 1,1¹-(alkylene)bis(5 - arylbiguanides) and acid-addition salts thereof, and to disinfecting or sanitizing compositions containing same.

The 1,1¹ - (alkylene)bis(5 - arylbiguanides) of the instant invention are represented in the free base form by the structural formula



Formula I

wherein C_nH_{2n} represents a bivalent alkylene bridge in which the free valance bonds are on two different carbon atoms and n is an integer from 2 to 12 inclusive, and Q and Q¹ each represent substituted phenyl having the structural formula



Formula Ia

wherein Y is hydrogen, halogen, trifluoromethyl, nitro, lower alkyl—O—, lower alkyl—S—, lower alkyl—SO— or lower alkyl—SO_2—; Z is hydrogen, halogen, nitro, lower alkyl or lower alkyl—O—; R is alkyl, halo-lower alkyl, lower alkenyl, benzyl, *ar*-halobenzyl, *ar*-nitrobenzyl, *ar*-lower alkylbenzyl, *ar*-lower alkoxybenzyl cyclohexyl, phenyl, lower alkylphenyl, nitrophenyl, lower alkoxyphenyl, halophenyl or, when neither of Y and Z is nitro, *ar*-aminobenzyl or aminophenyl; and X is —S—, —SO— or —SO_2—.

As will be seen from the identity of the radical X in the formula I above, all of our new compounds are sulphides, sulphoxides, or sulphones.

The bivalent alkylene bridge, C_nH_{2n}, in Formula I above is preferably polymethylene, represented by —$(CH_2)_n$— or equivalently by —$(CH_2)_{2-12}$—, but also includes branched chain alkylene bridges. Thus, C_nH_{2n} includes the alpha, omega divalent unbranched radicals ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene, and dodecamethylene, and

also includes for example the branched divalent radicals 1,2-propylene, 1,4-pentylene and 1,10-dodecamethylene.

The term "lower" used in connection with the choices for the radical R is used in each instance to indicate that not more than six carbon atoms are present in the lower alkyl, lower alkenyl or lower alkoxy group which is referred to.

In Formula Ia, when R is alkyl, there are included branched and unbranched alkyls of lower, intermediate, and higher molecular weight, preferably alkyl having 1—18 carbon atoms, and thus including, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-amyl, isohexyl, n-octyl, n-dodecyl, n-hexadecyl and n-octadecyl. Halo-lower alkyl includes, for example, 2-chloroethyl, 2-bromoethyl and trifluoromethyl. Lower alkenyl includes allyl and methallyl. The substituted benzyl radicals referred to in the definition of R, viz. *ar*-halobenzyl, *ar*-lower alkoxybenzyl, *ar*-nitrobenzyl, *ar*-aminobenzyl, and ar-lower alkylbenzyl, are of course benzyl radicals containing respectively halogen, lower alkoxy, nitro, amino, and lower alkyl substituents in the benzene ring. Preferably, one or two such substituents are present. These include, for example, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3,4-dichlorobenzyl, 4-bromobenzyl, 2,5-dibromobenzyl, 3-fluorobenzyl, 2,4-difluorobenzyl, 4-iodobenzyl, 2-chloro-4-bromobenzyl, 3-methoxybenzyl, 2-ethoxybenzyl, 2,4-dimethoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-aminobenzyl, 4-methylbenzyl and 2-methylbenzyl. The substituted phenyl radicals within the definition of R, viz. lower alkylphenyl, nitrophenyl, lower alkoxyphenyl, halophenyl, and aminophenyl, preferably contain 1 or 2 of the respective substituents in the ring and include for example 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2,4-dinitrophenyl, 4-methoxyphenyl, 2-methoxyphenyl, 3-ethoxyphenyl, 3,5-dimethoxyphenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3-bromophenyl, 3,4-dibromophenyl, 4-fluorophenyl, 4-iodophenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl and 2,4-diaminophenyl.

The symbol Y in Formula Ia represents hydrogen; halogen, i.e. fluorine, chlorine, bromine or iodine; trifluoromethyl; nitro; and lower alkyl—O—, lower alkyl—S—, lower alkyl—SO—, and lower alkyl—SO_2—, in which the lower alkyl in each instance contains 1—6 carbon atoms such as methoxy, ethoxy, isopropoxy, n-butoxy, methylmercapto, ethylmercapto, n-propylmercapto, isobutylmercapto, n-hexylmercapto, methylsulphinyl, n-propylsulphinyl, isohexylsulphinyl, methylsulphonyl, ethylsulphonyl, n-butylsulphonyl and n-hexylsulphonyl.

The symbol Z in Formula Ia represents hydrogen; halogen, i.e. fluorine, chlorine, bromine or iodine; nitro; and lower alkyl and lower alkyl—O—, in which lower alkyl in each instance contains 1—6 carbon atoms, such as methyl, ethyl, isopropyl, n-butyl, isohexyl, methoxy, ethoxy, n-propoxy, isobutoxy and n-hexoxy.

The compounds of Formula I are basic substances which interact with one or two equivalents of an organic or inorganic acid to form the corresponding mono- or di-acid-addition salts. These acid-addition salts and the free bases of course have the common structural entity represented by the structural Formula I. The new compounds of this invention include both the free bases and the acid-addition salts thereof.

Representative acids for the formation of the acid-addition salts include formic acid, acetic acid, isobutyric acid, alpha-mercaptopropionic acid, trifluoroacetic acid, malic acid, fumaric acid, succinic acid, succinamic acid, glutamic acid, tartaric acid, oxalic acid, pyromucic acid, citric acid, lactic acid, glycolic acid, gluconic acid, saccharic acid, ascorbic acid, penicillin, benzoic acid, phthalic acid, salicylic acid, 3,5-dinitrobenzoic acid, anthranilic acid, cholic acid, 2-pyridinecarboxylic acid, 3-hydroxy-2-naphthoic acid, picric acid, quinic acid, tropic acid, 3-indoleacetic acid, barbituric acid, sulphamic acid, methanesulphonic acid, ethanesulphonic acid, isethionic acid, benzenesulphonic acid, *p*-toluenesulphonic acid, butylarsonic acid, methanephosphonic acid, acidic resins, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid, perchloric acid, nitric acid, sulphuric acid, phosphoric acid, hydrocyanic acid, phosphotungstic acid, molybdic acid and arsenic acid.

The acid-addition salts are prepared in conventional fashion, for instance either by direct mixing of the acid and the base or, when this is not appropriate, by dissolving either or both of the acid and the base separately in water or an organic solvent and mixing the two solutions, or by dissolving both the acid and the base together in a solvent. The resulting acid-addition salt is isolated by filtration, if it is insoluble in the reaction medium, or by evaporation of the reaction medium to leave the acid-addition salt as a residue.

Our new bases of Formula I and the mono- and di-acid-addition salts thereof have antibacterial and anti-fungal properties. Thus, when tested by standard serial dilution procedures, these compounds were found to have bactericidal, bacteriostatic, fungicidal, and fungistatic activity *in vitro*. Moreover, some of these compounds exhibited antiviral activity, and others had amebacidal activity. Illustrative biological data are given below in the examples.

The new bases of Formula I and the mono- and di-acid-addition salts thereof are useful

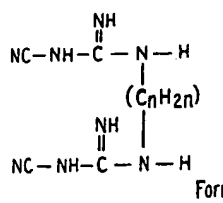
as disinfecting and sanitizing agents for application to living and non-living surfaces by conventional swabbing, padding, spraying, immersing and rinsing techniques. Depending on the partticular purpose involved, the compounds are incorporated in a suitable carrier and are usually used in aqueous solution, as in water or in aqueous detergent solutions, or in the form of solutions in organic solvents. Some of the compounds, for instance the 1,1¹-hexamethylene-bis[5-(4-alkylmercaptophenyl)biguanides] are especially useful for imparting an antibacterial and antifungal finish to cotton cloth.

The mono- and di-acid-addition salts of the bases of Formula I are useful not only as disinfecting and sanitizing agents, as above indicated, but are also useful as characterizing or identifying derivatives of the free bases and in isolation or purification procedures. Moreover, the acid-addition salts react with strong bases, such as alkali metal hydroxides, to generate the free bases, and accordingly all of the salts, regardless of considerations of solubility, toxicity or physical form of a particular species of acid-addition salt, are useful for the purposes of our invention since they are sources of the free bases.

It will be appreciated from the above that if one or more of the characteristics, such as solubility, molecular weight, physical appearance or toxicity of a given acid-addition salt render it unsuitable for the particular desired purpose, for example, use as an antibacterial agent or in an isolation or purification procedure, the acid-addition salt can be converted to the free base and then to another, more suitable acid-addition salt, for instance a pharmaceutically-acceptable salt when a pharmaceutical use is involved.

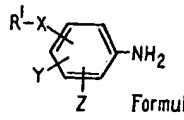
We particularly prefer those bases of Formula I, and the acid-addition salts thereof, wherein n is 5, 6 and 7, and Q and Q¹ are lower alkylmercaptophenyl and lower alkylmercaptohalophenyl, since the members of this group of compounds are especially useful as disinfecting and sanitizing agents.

The new compounds of our invention, except for those wherein R is *ar*-aminobenzyl or aminophenyl, for which a different method is used as described hereinbelow, are conveniently obtained by the process which comprises interacting a 1,1¹-(alkylene)bis(3-cyanoguanidine) having the structural formula



Formula II

with approximately two molecular proportions of an arylamine having the structural formula



Formula III

wherein X, Y, Z, and n have the same respective meanings stated hereinabove and R¹ is alkyl, halo-lower alkyl, lower alkenyl, benzyl, *ar*-halobenzyl, *ar*-nitrobenzyl, *ar*-lower alkylbenzyl, *ar*-lower alkoxybenzyl, cyclohexyl, phenyl, lower alkylphenyl, nitrophenyl, lower alkoxyphenyl or halophenyl, preferably in the form of a suitable acid-addition salt, such as the hydrochloride, of the arylamine. This process is carried out by heating the reactants together, preferably in the presence of an inert diluent such as 2-ethoxyethanol, 2-methoxyethanol or *o*-dichlorobenzene. We have found that it is generally convenient and satisfactory to reflux a mixture of the 1,1¹-(alkylene)bis(3-cyanoguanidine) (Formula II) and the hydrochloride of the arylamine (Formula III) in 2-ethoxyethanol until the reaction is complete. The reaction product, which is the dihydrochloride of a 1,1¹-(alkylene)bis(5-arylbiguanide) of Formula I, has low solubility in 2-ethoxyethanol and in water and is readily isolated.

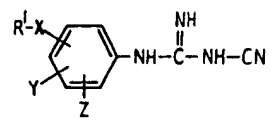
If desired, the dihydrochloride is converted to the corresponding free base form of Formula I by treatment with two molecular equivalents of a strong base such as sodium hydroxide. This free base can be used as such, or can be converted to any desired acid-addition salt.

In accordance with another feature of this invention, a second method for preparing our new compounds is provided which comprises interacting a suitable acid-addition salt, such as the dihydrochloride, of an alkylenediamine having the structural formula

$$H_2N—(C_nH_{2n})—NH_2$$

Formula IV

with approximately two molecular proportions of a 1-aryl-3-cyanoguanidine having the structural formula



Formula V

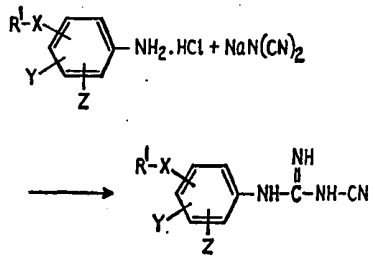
wherein R^1, X, Y, Z, and n have the same respective meanings stated hereinabove. This process is conveniently carried out by heating the reactants together, preferably in the presence of an inert diluent such as nitrobenzene. The reaction product, the dihydrochloride of a base of Formula I, has low solubility in nitrobenzene and is readily isolated by conventional means, as by collecting on a filter.

The species of Formula I wherein R is aminophenyl or aminobenzyl are obtained by reducing the corresponding nitrophenyl and nitrobenzyl compounds, for instance with iron and acid.

The species of Formula I which are sulphoxides can be prepared by the general methods above and also by oxidation of the corresponding sulphides, for instance by oxidation with one equivalent of either hydrogen peroxide or an organic per-acid such as peracetic acid or perbenzoic acid. The species of Formula I which are sulphones can be prepared by the general methods above and also by oxidation of the corresponding sulphoxides with one equivalent of either hydrogen peroxide or an organic per-acid, such as peracetic acid or perbenzoic acid.

The $1,1^1$ - (alkylene)bis(3 - cyanoguanidines) (Formula II) and the arylamines (Formula III) used as starting materials in the first of the foregoing methods for preparing our new compounds and the alkylenediamines (Formula IV) employed in the second method of preparation are all known classes of compounds, being readily prepared by known methods. For instance, the $1,1^1$-(alkylene)-bis(3-cyanoguanidines) (Formula II) are obtained conveniently by interaction of the appropriate alkylenediamine (Formula IV) dihydrochloride with two molecular proportions of sodium dicyanamide in boiling butanol.

The 1-aryl-3-cyanoguanidines of Formula V are novel compounds which may be prepared by interacting approximately equimolecular amounts of an appropriate arylamine (Formula III) acid-addition salt, such as the hydrochloride, and an alkali metal dicyanamide, such as sodium dicyanamide or potassium dicyanamide, in accordance with the following equation:



For example, the arylamine (Formula III) hydrochloride (or alternatively equivalent amounts of the arylamine and hydrogen chloride, as hydrochloric acid) and sodium dicyanamide are heated in a reaction medium of water, and the resulting product, which precipitates from solution, is isolated by filtration.

The chemical structures of the compounds of this invention followed from the modes of preparation and from elementary analyses of the products.

Our invention is illustrated by the following examples without, however being limited thereto. All percentages are by weight, unless otherwise stated.

EXAMPLE 1.

$1,1^1$ - Hexamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide]

A. A mixture of 22 g. of $1,1^1$-hexamethylene-bis(3-cyanoguanidine), 33 g. of 4-methylmercaptoaniline hydrochloride, and 290 ml. of 2-ethoxyethanol was refluxed for two hours, using a heated wax bath to prevent charring. While the mixture was being warmed up, all of the solid dissolved and shortly thereafter a solid separated from the solution in a thick mass. After the reflux period had ended, the reaction mixture was chilled and was then filtered. The tan solid thus collected was washed first with cold 2-ethoxyethanol and then with water, and was dried. There was thus obtained 40 g. of a tan powder which melted at 252—254° C. This solid was recrystallized from 21 volumes of 50 percent aqueous acetic acid. There was thus obtained 32 g. of cream colored powder which melted at 247—248° C. This product was the dihydrochloride of $1,1^1$-hexamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] (Formula I: R—X— = 4—CH_3—S—; Y = H; Z = H; n = 6), having the molecular formula $C_{24}H_{36}N_{10}S_2.2HCl$. The water-solubility of this compound was less than 0.25 percent at 25° C., and its solubility in 95 percent ethyl alcohol at 25° C. was less than 1 percent (weight/volume).

When this compound was tested for *in vitro* antibacterial and antifungal activity, the respective maximum effective aqeuous dilutions showing bacteriostatic (Bs), bactericidal (Bc), fungistatic (Fs) or fungicidal (Fc) activity against the indicated test organisms were as follows:

Staphylococcus aureus 209; Bs = 1—100,000; Bc = 1—100,000;

Erberthella typhi, Hopkins: Bs = 1—100,000; Bc = 1—100,000.

Trichophyton interdigitale: Fs = 1—133,000; Fc = 1—100,000;

Trichophyton mentagrophytes: Fs = 1—133,000; Fc = 1—40,000.

Aspergillus niger: Fs = 1—40,000; Fc = 1—20,000.

Trichophyton gypseum: Fs = 1—133,000; Fc = 1—100,000.

Monilia albicans: Fs = 1—133,000; Fc = 1—133,000.

Histoplasma capsulatum (mycelia phase): Fs = 1—200,000; Fc = 1—100,000.

Pityrosporum ovale: Fs = 1—1,000,000; Fc = 1—133,000.

This compound was found to have bacteriostatic activity against *Staphylococcus aureus* and *Escherichia coli* in aqueous solutions of soap, sodium lauryl sulphate, and nonylpolyglycol ether (Igepal CO—630—Antara Chemicals).

This compound was also found to be active *in vitro* against meningopneumonitis virus.

B. To a stirred, boiling solution of 39 g. of 1,1¹ - hexamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] di-hydrochloride in 830 ml. of 50 percent aqueous acetic acid there was added 830 ml. of 35 percent aqueous sodium hydroxide solution at a rate sufficient to maintain the reaction mixture at gentle reflux. After addition of the alkali was completed, the cloudy reaction mixture was cooled with stirring and was then filtered to collect the solid precipitate. The damp, light-brown filter cake was stirred with 600 ml. of cold water and the mixture was filtered. The beady, brown solid thus collected was washed with water. While being sucked free of water on the filter, the solid became sticky. The solid and the filter paper adhering to it were placed in 150 ml. of anhydrous ethyl alcohol, and the mixture was stirred vigorously while refluxing the alcohol for fifteen minutes. The mixture was chilled and was then filtered. The tan solid thus collected was washed with cold anhydrous ethyl alcohol and dried. The dry solid was ground in a mortar and the resulting powder was mixed with 50 ml. of boiling anhydrous ethyl alcohol. After chilling, the mixture was filtered and the collected solid was dried. There was thus obtained 20 g. of 1,1¹ - hexamethylene-bis[5 - (4 - methylmercaptophenyl)biguanide] (Formula I: R—X—=4—CH_2—S—; Y = H; Z = H; n=6), having the molecular formula $C_{24}H_{36}N_{10}S_2$. This product was a tan powder which melted at 169—172° C. The solubilities of this base in water and 95 percent ethyl alcohol were similar to those of the base dihydrochloride. The base was readily soluble in glacial acetic acid.

Cotton cloth was drawn through a 0.5 percent solution of this base in ethyl alcohol and was passed through a set of squeeze rolls which left on the cloth a weight of the solution amounting to 70 percent of the weight of the dry cloth. The wet cloth was then heated in an oven at 160° F. until dry. The cloth thus treated was then tested by the method described by Paul A. Majors in the American Dyestuff Reporter, *48*, No. 3, P 91—93 (1959) and was found to have an antibacterial coating which was highly resistant to washing, and still had effective antibacterial activity against *Staphylococcus aureus* after twenty-five washes with water and against *Brevibacterium ammoniagenes* after twenty washes with water.

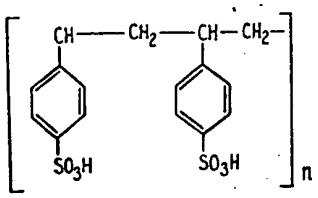
C. To a slurry to 5 g. of 1,1¹-hexamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] dihydrochloride in 50 ml. of water there was added 3.4 ml. of 35 percent aqueous sodium hydroxide solution and the resulting mixture was stirred vigorously for about seven hours in an ice bath. The mixture was filtered, and the tan solid thus collected was washed with water and was then sucked dry on the filter. There was thus obtained 3 g. of 1,1¹-hexamethylene-bis[5 - (4 - methylmercaptophenyl)biguanide]. This was the same product as that obtained in part B above.

D. To 61 g. of 1,1¹ - hexamethylene-bis[5 - (4 - methylmercaptophenyl)biguanide] there was added about 100 ml. of acteic acid while cooling the mixture in an ice bath. After addition of the acetic acid was completed, the mixture was stirred vigorously on a steam bath for several minutes. The mixture was then cooled, 1250 ml. of anhydrous diethyl ether was added, and the mixture was chilled overnight. The mixture was then filtered, and the tan solid thus collected was ground in a mortar and was washed with diethyl ether. The resulting solid product, which weighed 77 g., was recrystallized from three volumes of water containing decolorizing charcoal and a few drops of acetic acid. There was thus obtained 42 g. of 1,1¹-hexamethylene-bis[5 - (4 - methylmercaptophenyl)biguanide] diacetate as a pale yellow powder which melted at 91—97° C. The solubility of this product in water at 25° C. was less than 0.25 percent. In ethyl alcohol it was soluble up to 5 percent (weight/volume). It was not precipitated from a 5 percent solution in ethyl alcohol by addition of four volumes of water, the pH of the diluted solution being 6.7.

Tests of the *in vitro* activity of this diacetate against the bacteria and fungi mentioned in part A above showed results similar to those obtained using the dihydrochloride. In mice, for this diacetate the LD_{50} was 1750±480 mg./kg. (for the corresponding free base, 1420±390 mg./kg.) orally; was approximately 1500 mg./kg. intragastrically; and was approximately 150 mg./kg. intraperitoneally.

E. 23 g. of 1,1¹ - hexamethylene - bis-[5 - (4 - methylmercaptophenyl)biguanide] was dissolved in 300 ml. of dimethyl sulfoxide, and the slightly cloudy solution was filtered through a sintered glass filter. A piece of ice was added to the clear, yellow filtrate to cool it and ice water was added until the solution became faintly turbid. There

was then added 23 g. of an acidic ion exchange resin having the formula



("Amberlite" XE-66—"Amberlite" is a registered Trade Mark) to the solution and the mixture was shaken for four hours. The mixture was filtered, and the collected solid was washed well with water and was then dried in a vacuum oven at 95° C. for four hours. There was thus obtained 42.3 g. of the resin salt of 1,1¹ - hexamethylene-bis-[5 - (4 - methylmercaptophenyl)biguanide] as a tan powder which did not melt when heated at 300° C. This product had the molecular formula $C_{24}H_{36}N_{10}S_2.(C_8H_8O_3S)_n$.

In hamsters, this resin salt was active against *Endamoeba criceti* at a dose level of 100 mg./kg./day.

EXAMPLE 2.

1,1¹ - Hexamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide]

A. A mixture of 7.55 g. of 4-methylmercaptoaniline and a solution of 6.09 g. of potassium dicyanamide in 50 ml. of water was warmed, and then 4.8 ml. of concentrated hydrochloric acid was added. The mixture was heated at 80° C. for fifteen minutes and was filtered while still hot. The brown solid thus collected was purified to yield a solid which melted at 210—212° C. This product was 1 - (4 - methylmercaptophenyl)-3-cyanoguanidine (Formula V: R—X—= 4—CH_3—S—; Y=H; Z=H), having the molecular formula $C_9H_{10}N_4S$.

B. A mixture of 3.3 g. of hexamethylenediamine dihydrochloride, 7.1 g. of 1 - (4-methylmercaptophenyl) - 3 - cyanoguanidine, and 35 ml. of nitrobenzene is heated at 150—160° C. for six hours and then the reaction mixture is filtered while still hot. The solid collected in this manner is recrystallized from 50 percent aqueous acetic acid, with charcoaling. There is thus obtained the dihydrochloride of 1,1¹ - hexamethylene-bis[5 - (4 - methylmercaptophenyl)biguanide], the same product as that described in part A of Example 1.

EXAMPLE 3.

1,1¹ - Hexamethylene - bis[5 - (4 - methylsulfonylphenyl)biguanide]

A mixture of 9.85 g. of 1,1¹ - hexamethylene - bis(3 - cyanoguanidine), 17 g. of 4-methylsulfonylaniline hydrochloride, and 170 ml. of water was refluxed for three and one-half hours. During this heating period, all of the solid dissolved. After the reflux period was completed, the slightly turbid reaction solution was chilled. A small amount of brown gummy material separated from solution. There was then added to the solution 170 ml. of saturated sodium chloride solution, and the mixture was allowed to stand at room temperature for several days. Then the grey gummy solid which had separated from solution was collected on a filter. This material was placed in 54 ml. of ethyl alcohol. The resulting mixture was boiled and then was cooled and filtered. The solid thus collected was washed with cold anhydrous ethyl alcohol and was sucked dry on the filter. There was obtained in this manner 7 g. of solid. This product was slurried in 14 ml. of cold water, the mixture was filtered, and the collected solid was dried to yield 6 g. of white powder. Recrystallization of 5 g. of this powder from 15 ml. of boiling water containing three drops of dilute hydrochloric acid, using decolorizing charcoal, yielded 4 g. of white solid which softened at 158° C. and had an indefinite melting point. This product was the dihydrochloride monohydrate of 1,1¹ - hexamethylene - bis[5 - (4 - methylsulfonylphenyl)biguanide] (Formula I: R—X—=4—CH_3—SO_2—; Y=H; Z=H; n=6), having the molecular formula $C_{24}H_{36}N_{10}O_4S_2.2HCl.H_2O$. This compound was soluble in water at 25° C. to the extent of 1 percent. The pH of the 1 percent aqueous solution was 6.5, and when this solution was adjusted to pH 7.0 by adding 0.1 N aqueous sodium hydroxide solution, no precipitate formed.

When this compound was tested for *in vitro* antibacterial and antifungal activity, the respective maximum effective aqueous dilutions showing bacteriostatic (Bs), bactericidal (Bc), fungistatic (Fs) or fungicidal (Fc) activity against the indicated test organisms were as follows: *Staphylococcus aureus* 209, Bs=1—10,000; Bc=1—1,000; *Eberthella typhi*, Hopkins: Bs=1—1,000; Bc=less than 1—1,000; *Trichophyton mentagrophytes*: Fs=1—1,000; Fc=less than 1—1,000. *Aspergillus niger*: Fs=less than 1—1,000. *Monilia albicans*: Fs=1—1,000; Fc=less than 1—1,000.

EXAMPLE 4.

1,1¹ - Hexamethylene - bis[5 - (4 - methylsulphonylphenyl)biguanide]

To a slurry of 10 g. of 1,1¹ - hexamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] in 50 ml. of water at 20° C. there was added with stirring 11 ml. of 40 percent peracetic acid, cooling being used to prevent the temperature of the reaction mixture from rising above 40° C. After the reaction mixture had been stirred for about three and one-half hours, it was chilled and then filtered to remove 1.35 g. of unreacted 1,1¹ - hexamethylene - bis[5 - (4 - methyl-

mercaptophenyl)biguanide]. To the filtrate there was added 50 ml. of saturated sodium chloride solution and the mixture was allowed to stand for two days, during which time the gummy precipitate present solidified. After chilling the mixture, it was filtered to collect the solid, which was then washed with water and dried. This solid which weighed 7.5 g., was recrystallized from water, using decolorizing charcoal, to obtain a white powder. This product was $1,1^1$ - hexamethylene-bis[5 - (4 - methylsulphonylphenyl)biguanide] dihydrochloride monohydrate, the same compound as that described above in part A of Example 3.

EXAMPLE 5.

$1,1^1$ - Pentamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide]

A mixture of 9.2 g. of $1,1^1$ - pentamethylene - bis(3 - cyanoguanidine), 14.5 g. of 4 - methylmercaptoaniline hydrochloride, and 80 ml. of 2-ethoxyethanol was refluxed for two hours. The brown reaction mixture was filtered while still hot to collect as an insoluble solid product the dihydrochloride of $1,1^1$ - pentamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] (Formula I: R—X— = 4—CH_3—S—; Y = H; Z = H; n = 5), having the molecular formula $C_{23}H_{34}N_{10}S_2.2HCl$.

EXAMPLE 6.

$1,1^1$ - Heptamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide]

A mixture of 5 g. of $1,1^1$ - heptamethylene-bis(3 - cyanoguanidine), 7.07 g. of 4-methylmercaptoaniline hydrochloride, and 20 ml. of 2-ethoxyethanol was refluxed. After one-half hour of refluxing, all of the solid had dissolved and within another five minutes sufficient precipitate had come out of solution to make the mixture very thick. A 20 ml. portion of 2-ethoxyethanol was added to thin the mixture, and refluxing was continued to a total reflux time of one and one-half hours. The reaction mixture was then chilled and filtered. The solid thus collected was purified to yield 6 g. of white solid which was the dihydrochloride of $1,1^1$ - heptamethylene - bis[5 - (4-methylmercaptophenyl)biguanide] (Formula I: R—X— = 4—CH_3—S—; Y = H; Z = H; n = 7), having the molecular formula $C_{25}H_{38}N_{10}S_2.2HCl$.

EXAMPLE 7.

$1,1^1$ - Hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide]

A. A mixture of 32.2 g. of 4 - ethylmercaptoaniline hydrochloride and 20 g. of $1,1^1$ - hexamethylene - bis(3 - cyanoguanidine) in 300 ml. of 2 - ethoxyethanol was refluxed on a wax bath for two hours. As the mixture was warmed, all of the solid dissolved, and shortly thereafter a solid separated from the solution in a thick mass. After the reflux period was completed, the reaction mixture was chilled and then filtered. The tan solid collected on the filter was purified to yield 19 g. of white powder which melted at 236—238° C. This product was the dihydrochloride of $1,1^1$ - hexamethylene - bis[5 - (4-ethylmercaptophenyl)biguanide] (Formula I: R—X— = 4—C_2H_5—S—; Y = H; Z = H; n = 6), having the molecular formula $C_{26}H_{40}N_{10}S_2.2HCl$. The water-solubility of this compound was less than 0.25 percent at 25° C. and its solubility in 95 percent ethyl alcohol at 25° C. was less than 1 percent (weight/volume).

When this compound was tested for *in vitro* antibacterial and antifungal activity, the respective maximum effective dilutions showing bacteriostatic (Bs), bactericidal (Bc), fungistatic (Fs) or fungicidal (Fc) activity against the indicated test organisms were as follows: *Staphylococcus aureus* 209; Bs = 1—200,000; Bc = 1—80,000; *Eberthella typhi*, Hopkins: Bs = 1—1,000,000; Bc = 1—50,000; *Mycobacterium tuberculosis*, H37Rv: Bs = 1—50,000; Bc = 1—50,000; *Pseudomonas aeruginosa*: Bs = 1—100,000; Bc = 1—20,000. *Trichophyton mentagrophytes*: Fs = 1—133,000; Fc = 1—133,000. *Aspergillus niger*: Fs = 1—10,000; Fc = 1—10,000. *Monilia albicans*: Fs = 1—200,000; Fc = 1—100,000. *Pityrosporum ovale*: Fs = 1—400,000; Fc = 1—400,000. In dilute aqueous solutions of soap, sodium lauryl sulfate, and nonylphenylpolyglycol ether, this dihydrochloride was bacteriostatically active against *Staphylococuus aureus* and Escherichia coli. This compound at a concentration of 1.0 mg./ml. in dilute aqueous soap solution was active against the mildew organism *Chaetonium globosum*, Kunze; and at a concentration of 1.0 mg./ml. in a dilute aqueous solution of an organic sulfonate detergent, it was active against Streptococcus aureus, 209 and *Eberthella typhi*, Hopkins. This compound also showed activity against feline pneumonitis, canine distemper (Onderstepoort strain), rabies (Flury strain), and meningopneumonitis viruses. In hamsters, it was effective at 100 mg./kg. against *Endamoeba criceti*.

In mice, the LD_{50} of this dihydrochloride was approximately 350 mg./kg. intraperitoneally, was greater than 4000 mg./kg. orally, and greater than 2000 mg./kg. intragastrically.

B. To a slurry of 86 g. of $1,1^1$ - hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide] dihydrochloride in 860 ml. of refluxing methyl alcohol there was added 23 ml. of 35 percent aqueous sodium hydroxide solution. Practically all of the solid dissolved, and the resulting cloudy solution was treated with decolorizing charcoal and filtered through a diatomaceous earth filter

("Filter-Cel"—registered Trade Mark). The filtrate was chilled with occasional stirring, and the solid which separated from solution was collected on a filter, and was washed thoroughly with methyl alcohol and then with water, and dried. The resulting product, a cream colored powder which weighed 69 g., was recrystallized from 10 volumes of methyl alcohol, using decolorizing charcoal and a filter of "Filter-Cel". There was thus obtained 58 g. of white powder which melted at 147—149° C. This product was 1,1¹-hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide] (Formula I: R—X—= 4—C_2H_5—S—; Y=H; Z=H; n=6), having the molecular formula $C_{26}H_{40}N_{10}S_2$. The solubility of this compound at 25° C. in each of water and 0.5 N hydrochloric acid was less than 0.25 percent, and its solubility in ethyl alcohol was less than 1 percent (weight/volume).

In hamsters, this base was effective at 50 mg./kg./day against *Endamoeba criceti.*

An ethanolic solution of this base was padded onto cotton cloth and the treated cloth was tested for antibacterial activity against *Brevibacterium ammoniagenes,* following the Majors method referred to in part B of Example 1. Before washing, the treated cloth was completely inhibitory to the growth of *Brevibacterium ammoniagenes;* and after five launderings the treated cloth still had some antibacterial activity.

C. To a mixture of 79 g. of 1,1¹-hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide] and 32.6 g. of 85.2 percent *dl*-lactic acid there was added 395 ml. of boiling water. This mixture was heated on a steam bath until all of the solid had dissolved, and then decolorizing charcoal was added and the mixture was filtered through "Filter-Cel". The filtrate was chilled overnight, and the solid which separated from solution was collected on a filter. The off-white solid, which weighed 81 g., was recrystallized from 2 volumes of water to yield 74 g. of white powder which melted at 92—99° C. This product was 1,1¹ - hexamethylene - bis 5 - (4 - ethylmercaptophenyl)-biguanide di-*dl*-lactate. The water-solubility of this compound was less than 0.25 percent at 25° C. and was about 1 percent in warm water. In ethyl alcohol, it was soluble to the extent of about 1 percent, being precipitated from the 1 percent alcoholic solution by addition of 4 volumes of water.

When added at a concentration of 1—100,000 to urine, this compound inhibited the growth of *Escherichia coli.*

In mice the LD_{50} of this compound was approximately 6000 mg./kg. (twenty-four hour test) and approximately 5000 mg./kg. (seven-day test) orally, and approximately 9 mg./kg. intravenously.

D. To a mixture of 11.1 g. of 1,1¹-hexamethylene - bis - [5 - (4 - ethylmercaptophenyl)biguanide] and 8.0 g. of 10-undecylenic acid there was added 60 ml. of boiling isopropyl alcohol. The resulting mixture was heated on a steam bath, decolorizing charcoal was added, and the hot mixture was filtered. The amber colored filtrate was chilled, with occasional stirring and was then filtered to collect the cream colored solid which separated from solution. The solid on the filter was washed with isopropyl alcohol, sucked partially dry, and then dried in a vacuum oven at 25° C. There was thus obtained 11.6 g. of cream-colored powder which melted at 68—70° C. This product was 1,1¹ - hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide] di - (10 - undecylenate), having the molecular formula $C_{26}H_{40}N_{10}S_2.2C_{11}H_{20}O_2$. The solubility of this compound in water at 25° C. was less than 0.25 percent, and its solubility in ethyl alcohol at 25° C. was less than 1 percent (weight/volume).

E. To a slurry of 3 g. of 1,1¹ - hexamethylene - bis[5 - (4 - ethylmercaptophenyl)-biguanide] dihydrochloride in 30 ml. or refluxing methyl alcohol there was added 0.8 ml. of 0.01 M aqueous sodium hydroxide solution. On this addition, practically all of the solid dissolved. The slightly cloudy solution was mixed with decolorizing charcoal and filtered. The filtrate was chilled and then filtered through "Filter-Cel" to collect 2.3 g. of solid. 1 g. of this product, which was 1,1¹ - hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide], was dissolved in 2 ml. of warm acetic acid, 20 ml. of anhydrous diethyl ether was added to the solution, and the mixture was allowed to stand, with occasional stirring, at room temperature until the gummy yellow precipitate present had solidified. The solid was collected on a filter; washed well with anhydrous diethyl ether, and dried. This product weighed 0.82 g.; a 0.44 g. portion of it was recrystallized from 3 ml. of isopropyl alcohol, using decolorizing charcoal, to yield 0.15 g. of solid which melted at 165—167° C. This product was 1,1¹-hexamethylene - bis[5 - (4 - ethylmercaptophenyl)-biguanide] diacetate, having the molecular formula $C_{26}H_{40}N_{10}S_2.2C_2H_4O_2$.

F. A mixture of 1 g. of 1,1¹ - hexamethylene - bis[5 - (4 - ethylmercaptophenyl)-biguanide], 0.394 g. of ethanesulfonic acid, and 3 ml. of anhydrous isopropyl alcohol was heated on a steam bath. The resulting solution was allowed to cool slowly and the white solid which separated from solution was collected on a filter, washed with isopropyl alcohol and with diethyl ether, and dried. There was thus obtained 1.12 g. of 1,1¹ - hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide] di(methanesulphonate), having the molecular formula $C_{26}H_{40}N_{10}S_2.2C_2H_6SO_3$, which melted at

175—180° C. This salt was soluble in water at 25° C. to the extent of at least 1 percent.

G. Using a procedure similar to that in part F above, 1 g. of 1,1¹ - hexamethylene-bis 5 - (4 - ethylmercaptophenyl) - biguanide) was interacted with 0.350 g. of methane sulphonic acid to yield 1.06 g. of 1,1¹ - hexamethylene - bis[5 - (4 - ethylmercaptophenyl)-biguanide] di(methanesulphonate), having the molecular formula $C_{26}H_{40}N_{10}S_2.2CH_4SO_3$, which melted over a wide range, from 80—150° C. This salt was soluble in water at 25° C. to the extent of at least 1 percent.

Example 8.

1,1¹ - Hexamethylene - bis[5 - (4 - ethylsulphonylphenyl)biguanide]

A. To a slurry of 31.2 g. of 1,1¹ - hexamethylene - bis - [5 - (4 - ethylmercaptophenyl)biguanide] dihydrochloride in 150 ml. of water at room temperature (about 25° C.), there was added dropwise 41.3 ml. of 40 percent peracetic acid, an ice bath being used as necessary to keep the temperature of the reaction mixture from rising about 40° C. The reaction mixture was stirred at room temperature for several hours. Decolorizing charcoal was added, and the mixture was filtered. The filtrate was chilled and 300 ml. of saturated aqueous sodium chloride solution was added to it. The gum which separated from solution was collected and washed with 100 ml. of saturated aqueous sodium chloride solution. The gum was dissolved in methyl alcohol, decolorizing charcoal was added, and the mixture was filtered. Anhydrous calcium sulphate and decolorizing charcoal were added to the filtrate, and the mixture was filtered. The solvent was evaporated from the filtrate under reduced pressure to yield 34.8 g. of a foamy solid residue. This product was the dihydrochloride of 1,1¹ - hexamethylene-bis-[5 - (4 - ethylsulphonylphenyl)biguanide] (Formula I: R—X—=4—C_2H_5—SO_2—; Y=H; Z=H; n=6), having the molecular formula $C_{26}H_{40}N_{10}O_4S_2.2HCl$.

B. The 1,1¹ - hexamethylene - bis[5 - (4-ethylsulphonylphenyl)biguanide] dihydrochloride was dissolved in methyl alcohol, decolorizing charcoal was added, and the mixture was filtered. The filtrate was chilled and 8 ml. of 35 percent aqueous sodium hydroxide solution was added. The solid which precipitated from solution was collected on a filter, washed with water and with anhydrous diethyl ether, and dried at 50° C. for several hours. The dry solid, which weighed 23.3 g., was dissolved in 480 ml. of hot N,N-dimethylformamide, decolorizing charcoal was added, and the mixture was filtered. The filtrate was chilled, sufficient water was added to initiate crystallization, and the mixture was chilled for several hours. The solid which separated from solution was collected on a filter and dried. There was thus obtained 14.5 g. of off-white powder which melted at 197—198° C. This product was 1,1¹-hexamethylene - bis[5 - (4 - ethylsulphonylphenyl)-biguanide] (Formula I: R—X—=4—C_2H_5—SO_2—; Y=H; Z=H; n=6), having the molecular formula $C_{26}H_{40}N_{10}O_4S_2$. A further crop of 2.5 g. of the base was recovered from the filtrate from collection of the first crop.

This base was soluble at 25° C. in a mixture of equal volumes of water and 0.5 N aqueous hydrochloric acid solution to the extent of 5 percent. The pH of a 1 percent solution in the dilute acid solution was 2.1.

Example 9.

1,1¹ - Hexamethylene - bis[5 - (4 - n-propylmercaptophenyl)biguanide]

A. A mixture of 20 g. of 1,1¹ - hexamethylene - bis (3 - cyanoguanidine) and 34.5 g. of 4 - n - propylmercaptoaniline hydrochloride in 270 ml. of 2-ethoxyethanol was refluxed on an oil bath. While the mixture was being warmed up, all of the solid went into solution and shortly thereafter when a solid began to separate from solution another 50 ml. portion of 2-ethoxyethanol was added. After a total period of refluxing of two hours, the reaction mixture was chilled and then filtered to collect the solid which had separated. This solid was purified to yield 20 g. of cream-coloured powder which melted at 238—240° C. This product was the dihydrochloride of 1,1¹ - hexamethylene - bis-[5 - (4 - n - propylmercaptophenyl)biguanide] (Formula I:

R—X—=4—$CH_3CH_2CH_2$—S—; Y=H; Z=H; n=6), having the molecular formula $C_{28}H_{44}N_{10}S_2.2HCl$. The water solubility of this compound was less than 0.25 percent at 25° C., and its solubility in ethyl alcohol was less than 1 percent (weight/volume).

B. 203 g. of 1,1¹ - hexamethylene - bis-[5 - (4 - n - propylmercaptophenyl)biguanide] dihydrochloride was slurried in 2030 ml. of methyl alcohol and the mixture was refluxed on a steam bath. To the refluxing mixture there was gradually added during a period of five minutes 50 ml. of 35 percent aqueous sodium hydroxide solution. The resulting solution was treated with decolorizing charcoal and filtered through "Filter-Cel". The filtrate was chilled with occasional stirring, and the light tan solid which separated from solution was collected on a filter, washed with cold methyl alcohol, and sucked dry on the filter. The collected solid, which weighed 148.5 g., was recrystallized from 445 ml. of benzene, using decolorizing charcoal, and the product was dried at 65° C. under reduced pressure (17 mm.) for eight hours. There was thus obtained 103 g. of cream coloured solid which melted at 124—133° C. and had a faint garlic-like odour. This product

was 1,1¹ - hexamethylene - bis[5 - (4 - n-propylmercaptophenyl)biguanide] (Formula I: R—X—=4—$CH_3CH_2CH_2$—S—; Y=H; Z=H; n=6), having the molecular formula $C_{28}H_{44}N_{10}S_2$. The solubility of this compound in water was less than 0.25 percent at 25° C. and its solubility in ethyl alcohol at 25° C. was less than 1 percent. It was readily soluble in aqueous lactic acid solution.

C. A mixture of 139.3 g. of 1,1¹ - hexamethylene - bis[5 - (4 - n - propylmercaptophenyl)biguanide], 53.3 g. of 85.2 percent lactic acid, and 280 ml. of water was heated and stirred until most of the solid had dissolved. The hot mixture was filtered, and the filtrate was chilled in a refrigerator. The solid which separated from the solution was collected on a filter, washed with cold water, and sucked partially dry on the filter. The damp solid was recrystallized from 344 ml. of water, using decolorizing charcoal. There was thus obtained 103 g. of white powder which melted at 97—105° C. and had a faint garlic-like odour. This product was 1,1¹-hexamethylene - bis[5 - (4 - n - propylmercaptophenyl)biguanide] di - *dl* - lactate, having the molecular formula

$$C_{28}H_{44}N_{10}S_2.2C_3H_6O_3.$$

The solubility of this compound in water at 25° C. was less than 0.25 percent; it was soluble to the extent of about 1 percent in warm water, and did not separate readily when the warm solution was cooled. It was soluble to the extent of 5 percent (weight/volume) in ethyl alcohol; and it was precipitated from a 5 percent solution in ethyl alcohol by addition of four volumes of water.

D. A mixture of 2 g. of 1,1¹ - hexamethylene - bis[5 - (4 - n - propylmercaptophenyl)biguanide] and 2 ml. of glacial acetic acid was warmed on a steam bath, and to the resulting solution there was added with stirring 50 ml. of anhydrous diethyl ether. After the mixture had stood for two hours, it was filtered. The white solid thus collected was washed with diethyl ether and dried, and was then mixed with 10 ml. of anhydrous diethyl ether and allowed to stand overnight. The mixture was then filtered, and the solid thus collected was washed with anhydrous ethyl ether and dried. There was obtained 2.05 g. of white solid which melted at 190—195° C. with decomposition. This product was 1,1¹ - hexamethylene - bis[5 - (4 - n - propylmercaptophenyl)biguanide] diacetate, having the molecular formula $C_{28}H_{44}N_{10}S_2.2C_2H_4O_2$. This salt was readily soluble in warm water.

In mice, the LD_{50} of the dilactate was greater than 8000 mg./kg. (twenty-four hour test) and approximately 7000 mg./kg. (seven day test) orally and approximately 11 mg./kg. intravenously.

EXAMPLE 10.

1,1¹ - Hexamethylene - bis[5 - (4 - n - propylsulphonylphenyl)biguanide]

A. To a slurry of 46.4 g. of 1,1¹ - hexamethylene - bis[5 - (4 - n - propylmercaptophenyl)biguanide] dihydrochloride in 232 ml. of water at room temperature there was added dropwise 46.3 ml. of 40 percent peracetic acid, the reaction mixture being cooled to keep the temperature from rising above 40° C. After addition of the peracetic acid was completed, the reaction mixture was stirred for one hour at room temperature and was then filtered to remove a small amount of insoluble material which was discarded. The filtrate was stirred at room temperature for two hours and at 0° C. for one hour. To the clear reaction solution there was added 250 ml. of saturated aqueous sodium chloride solution, whereupon a pink gum precipitated. The liquid was decanted away from the gum, and after washing the gum with 50 ml. of saturated aqueous sodium chloride solution it was dissolved in methyl alcohol. Decolorizing charcoal was added to the solution, which was then filtered. The filtrate was dried over anhydrous calcium sulphate, and after removal of the drying agent the solvent was evaporated from the solution under reduced pressure to yield as a residue 58.5 g. of the dihydrochloride of 1,1¹ - hexamethylene - bis[5 - (4-n - propylsulphonylphenyl)biguanide] (Formula I: R—X—=4—$CH_3CH_2CH_2$—SO_2—; Y=H; Z=H; n=6) as a light pink paste. Just sufficient methyl alcohol to dissolve the paste was added, and to the resulting solution was added 13 ml. of 35 percent aqueous sodium hydroxide solution. The resulting mixture was chilled and the solid which separated from solution was collected on a filter and washed with methyl alcohol and with anhydrous diethyl ether. The solid was then dried at 65° C. in a vacuum oven for four hours. There was thus obtained 41.2 g. of cream colored powder which melted at 200—201° C. with decomposition. This product was 1,1¹ - hexamethylene - bis[5 - (4-n - propylsulphonylphenyl)biguanide] (Formula I: R—X—=4—$CH_3CH_2CH_2$—SO_2—; Y=H; Z=H; n=6), having the molecular formula $C_{28}H_{44}N_{10}O_4S_2$. This compound was soluble to the extent of 10 percent in dilute hydrochloric acid. When 0.1 N aqueous sodium hydroxide solution was added to a 1 percent solution of pH 2.1 in dilute hydrochloric acid, a precipitate formed at pH 3.3.

EXAMPLE 11.

1,1¹ - Hexamethylene - bis[5 - (4 - n - butylmercaptophenyl)biguanide]

A. A mixture of 12 g. of 1,1¹ - hexamethylene - bis (3 - cyanoguanidine), 22.2 g. of 4 - n - butylmercaptoaniline hydrochloride and 88 ml. of 2-ethoxyethanol was stirred

and heated to reflux temperature on an oil bath. During this heating period, all of the solid dissolved, and shortly thereafter a heavy tan precipitate came out of solution. A 40 ml. portion of 2-ethoxyethanol was added to the mixture to facilitate stirring. After a total period of two hours of refluxing, the reaction mixture was chilled and filtered. The tan solid thus collected was purified to yield 19 g. of white powder which melted at 251—253° C. This product was the dihydrochloride of 1,1¹ - hexamethylene - bis[5 - (4 - n - butylmercaptophenyl)biguanide] (Formula I:

R—X—=4—$CH_3CH_2CH_2CH_2$—S—; Y=H; Z=H; n=6), having the molecular formula $C_{30}H_{48}N_{10}S_2.2HCl$. The solubility of this compound in water at 25° C. was less than 0.25 percent, and its solubility in ethyl alcohol at 25° C. was less than 1 percent (weight/volume).

B. A slurry of 126.5 g. of 1,1¹ - hexamethylene - bis[5 - (4 - n - butylmercaptophenyl)biguanide] dihydrochloride in 1265 ml. of methyl alcohol was heated to reflux temperature on a steam bath, and then 31.6 ml. of 35 percent aqueous sodium hydroxide solution was gradually added over a period of five minutes. The resulting solution was treated with decolorizing charcoal and filtered through "Filter-Cel", and the filtrate was chilled. The solid which separated from solution was collected on a filter. This product, which weighed 99 g., was recrystallized from 400 ml. of methyl alcohol, using decolorizing charcoal, to yield 83 g. of cream coloured solid which melted at 107—109° C. and had a faint garlic-like odour. This product was 1,1¹-hexamethylene - bis[5 - (4 - n - butylmercaptophenyl)biguanide] (Formula I:

R—X—=4—$CH_3CH_2CH_2CH_2$—S—; Y=H; Z=H; n=6), having the molecular formula $C_{30}H_{48}N_{10}S$. The solubility of this compound in water at 25° C. was less than 0.25 percent, and its solubility in ethyl alcohol was less than 1 percent (weight/volume). It was very soluble in aqueous lactic acid solution.

C. To a mixture of 147 g. of 1,1¹-hexamethylene - bis - [5 - (4 - n - butylmercaptophenyl)biguanide] and 250 ml. of anhydrous isopropyl alcohol there were added 60.2 g. of 85.2 percent racemic lactic acid and 265 ml. of anhydrous isopropyl alcohol. The resulting mixture was heated on a steam bath until practically all of the solid had dissolved. The hot reaction mixture was filtered, and the filtrate was chilled in a refrigerator for three days. The solid which had separated from solution was collected on a filter, washed with cold anhydrous isopropyl alcohol, and dried, first at room temperature and then for eight hours at 60° C. under reduced pressure. There was thus obtained 82 g. of white powder which melted at 130—133° C. and had a faint garlic-like odour. This product was 1,1¹ - hexamethylene - bis - [5 - (4 - n - butylmercaptophenyl)biguanide] di - *dl* - lactate, having the molecular formula

$C_{30}H_{48}N_{10}S_2.2C_3H_6O_3$.

This compound was soluble in water at 25° C. to the extent of 10 percent. The pH of a 1 percent aqueous solution was 6.5; when this solution was adjusted to pH 7.0 by addition of 0.1 N aqueous sodium hydroxide solution, no precipitate was formed.

In mice, the LD_{50} of this compound was approximately 11 mg./kg. intravenously, and greater than 4000 mg./kg. orally.

EXAMPLE 12.

1,1¹ - Hexamethylene - bis[5 - (4 - n - butylsulphonylphenyl)biguanide]

To a stirred slurry of 61.1 g. of 1,1¹-hexamethylene - bis[5 - (4 - n - butylmercaptophenyl)biguanide] in 306 ml. of water at room temperature there was added dropwise 59 ml. of 40 percent peracetic acid. During this addition, the temperature of the reaction mixture was maintained below 40° C. by means of cooling with an ice-bath. After the addition of the peracetic acid was completed, the reaction mixture was stirred at room temperature for four hours. Another portion (14.7 ml.) of 40 percent peracetic acid was then added and the mixture was stirred for several hours more. The reaction mixture was cooled and stirred at 0° C., and 300 ml. of saturated aqueous sodium chloride solution was added, thereby causing separation of a pink gum. The supernatant liquid was decanted from this gum and after washing with 100 ml. of saturated aqueous sodium chloride solution it was dissolved in methyl alcohol. Decolorizing charcoal was added to the alcoholic solution and the resulting mixture was filtered. The filtrate was dried over anhydrous calcium sulfate, and the dried solution was mixed with decolorizing charcoal and filtered. The solvent was evaporated from the filtrate under reduced pressure, thus yielding 80.1 g. of pink gum as a residue. This product was the dihydrochloride of 1,1¹ - hexamethylene - bis[5 - (4 - n - butylsulphonylphenyl)biguanide] (Formula I: R—X—=4—$CH_3CH_2CH_2CH_2$—SO_2—; Y=H; Z=H; n=6), having the molecular formula $C_{30}H_{48}N_{10}O_4S_2.2HCl$. This salt was dissolved in the minimum amount of methyl alcohol and the resulting solution was filtered to remove a small amount of insoluble material. The filtrate was stirred and cooled in an ice bath, and 16 ml. of 35 percent aqueous sodium hydroxide solution was added. The solid which separated from solution was collected on a filter, washed with water and with anhydrous diethyl ether, and dried for several hours at 70° C. in an oven. The resulting solid, which weighed 47.3 g., was dissolved in 5.2 volumes of hot N,N-dimethyl-

formamide, and after adding water the solution was cooled. The solid which separated from solution was collected on a filter and dried. There was thus obtained 25.6 g. of product. A 10.2 g. crop of product was recovered from the mother-liquor above. The two crops were combined and recrystallized from N,N - dimethylformamide-water to yield 25.4 g. of solid which melted at 183—185° C. This product was 1,1¹ - hexamethylene-bis[5 - (4 - n - butylsulphonylphenyl)-biguanide] (Formula I: R—X—= 4—$CH_3CH_2CH_2CH_2—SO_2$—; Y=H; Z=H; n=6), having the molecular formula $C_{30}H_{48}N_{10}O_4S_2$. The solubility of this base in a mixture of 0.50 ml. of 0.5 N hydrochloric acid and 19.50 ml. of water at 25° C. was less than 0.25 percent; and its solubility in ethyl alcohol at 25° C. was less than 1 percent.

EXAMPLE 13.

1,1¹ - Hexamethylene - bis[5 - (4 - n - amylmercaptophenyl)biguanide]

A mixture of 26 g. of 1,1¹ - hexamethylene-bis(3 - cyanoguanidine), 51 g. of 4 - n - amylmercaptoaniline hydrochloride, and 510 ml. of 2-ethoxyethanol was refluxed for two hours. During this period, all of the solids dissolved to produce a dark red solution, and then a precipitate separated. After completion of the reflux period, the reaction mixture was chilled and then filtered. The pink solid thus collected, which weighed 50.5 g., was purified to yield 37.9 g. of cream-coloured solid which melted at 242—246° C. This product was the dihydrochloride of 1,1¹-hexamethylene - bis[5 - (4 - n - amylmercaptophenyl)biguanide] (Formula I: R—X—= 4—$CH_3CH_2CH_2CH_2CH_2—S$—; Y=H; Z=H; n=6), having the molecular formula $C_{32}H_{52}N_{10}S_2.2HCl$. The solubility of this compound in water at 25° C. was less than 0.25 percent, and its solubility in ethyl alcohol was less than 1 percent (weight/volume).

When this compound was tested for *in vitro* antibacterial and antifungal activity, the respective maximum effective aqueous dilutions showing fungistatic (Fs) or fungicidal (Fc) activity against the indicated test organisms were as follows: *Trichophyton mentagrophytes*: Fs=1—10,000; Fc=1—10,000. *Aspergillus niger*: Fs=1—10,000; Fc=1—10,000. *Monilia albicans*: Fs=1—10,000; Fc=1—10,000. This compound was active *in vitro* against rabies, meningopneumonitis, and feline pneumonitis viruses.

EXAMPLE 14.

1,1¹ - Hexamethylene - bis[5 - (4 - methylmercapto - 3 - chlorophenyl)biguanide]

A mixture of 38 g. of 4 - methylmercapto-3 - chloroaniline hydrochloride, 23.4 g. of 1,1¹ - hexamethylene - bis(3 - cyanoguanidine), and 127 ml. of 2-ethoxyethanol was stirred and refluxed at 130° C. for fifteen minutes. Decolorizing charcoal was then added, and the reaction mixture was filtered while still hot. The filtrate thus obtained was distilled under reduced pressure to remove the 2-ethoxyethanol. The semi-solid thus obtained was stirred in 150 ml. of n-butyl alcohol and the mixture was filtered, using a steam-heated filter and coarse filter paper. The solid collected in this manner was dried at 100° C. in a vacuum oven. The dry solid, which weighed 36.3 g., was purified to yield 16.2 g. of solid which melted at 222—225° C. This product was the dihydrochloride of 1,1¹-hexamethylene - bis[5 - (4 - methylmercapto-3 - chlorophenyl)biguanide] (Formula I: R—X—=4—CH_2—S—; Y=3—Cl; Z=H; n=6). The solubility of this compound in water at 25° C. was less than 0.25 percent, and its solubility in ethyl alcohol at 25° C. was less than 1 percent (weight/volume).

When this compound was tested for *in vitro* antibacterial and antifungal activity, the respective maximum effective aqueous dilutions showing bacteriostatic (Bs), bactericidal (Bc), fungistatic (Fs) or fungicidal (Fc) activity against the indicated test organisms were as follows: *Staphylococcus aureus* 209: Bs=1—1,000,000; Bc=1—400,000; *Eberthella typhi*, Hopkins: Bs=1—1,000,000; Bc=1—200,000. *Pseudomonas aeruginosa*: Bs=1—130,000; Bc=1—40,000. *Clostridium welchii*, M: Bs=1—1,200,000; Bc=1—1,200,000; *Trichophyton mentagrophytes*: Fs=1—100,000; Fc=1—100,000. *Aspergillus niger*: Fs=1—10,000; Fc=less than 1—1,000. *Monilia albicans*: Fs=1—100,000; Fc=1—10,000.

EXAMPLE 15.

1,1¹ - Hexamethylene - bis[5 - (4 - ethylmercapto - 3 - chlorophenyl)biguanide]

A mixture of 37 g. of 1,1¹ - hexamethylene-bis(3 - cyanoguanidine), 64.1 g. of 4 - ethylmercapto - 3 - chloroaniline hydrochloride, and 300 ml. of 2-ethoxyethanol was refluxed at 130° C. for twenty minutes. Decolorizing charcoal was added and the reaction mixture was filtered while still hot. The 2-ethoxyethanol was distilled from the filtrate under reduced pressure. The 144 g. of pink, pasty solid obtained as a residue was purified to yield 21.9 g. of off-white powder which melted at 214—215° C. This product was the dihydrochloride of 1,1¹ - hexamethylene - bis-[5 - (4 - ethylmercapto - 3 - chlorophenyl)-biguanide] (Formula I: R—X—= 4—C_2H_5—S—; Y=3—Cl; Z=H; n=6), having the molecular formula

$C_{26}H_{38}Cl_2N_{10}S_2.2HCl$.

The solubility of this salt in water at 25° C. was less than 0.25 percent, and its solubility in ethyl alcohol at 25° C. was less than 1 percent (weight/volume).

EXAMPLE 16.

1,1¹ - Hexamethylene - bis[5 - (4 - n - propylmercapto - 3 - chlorophenyl)biguanide]

A mixture of 31 g. of 1,1¹ - hexamethylene-bis(3 - cyanoguanidine), 56.8 g. of 4 - n-propylmercapto - 3 - chloroaniline hydrochloride, and 250 ml. of 2-ethoxyethanol was stirred and refluxed for twenty minutes. Decolorizing charcoal was then added and the mixture was filtered while still hot. The solvent was evaporated from the filtrate under reduced pressure. The 126.5 g. of pasty, pink solid obtained as a residue was slurried in 8.5 volumes of isoamyl alcohol, and the slurry was filtered. The collected solid was washed with diethyl ether and dried. The dry solid, which weighed 48.8 g., was ground and slurried in anhydrous diethyl ether, the slurry was filtered, and the collected solid was washed with anhydrous diethyl ether and dried. There was thus obtained 47.2 g. of pink powder which melted at 226—228° C. This product was the dihydrochloride of 1,1¹-hexamethylene - bis[5 - (4 - n - propylmercapto - 3 - chlorophenyl)biguanide] (Formula I:

R—X—=4—$CH_3CH_2CH_2$—S—;
Y=3—Cl; Z=H; n=6), having the molecular formula $C_{28}H_{42}Cl_2N_{10}S_2.2HCl$. The solubility of this salt in water at 25° C. was less than 0.25 percent; and its solubility in ethyl alcohol was less than 1 percent.

EXAMPLE 17.

1,1¹ - Tetramethylene - bis[5 - (4 - n - propylsulphinyl - 3 - chlorophenyl)biguanide]

A. A slurry of 20 g. of 4 - n - propylmercapto - 3 - chloroaniline hydrochloride in 280 ml. of a mixture (by volume) of 3 parts of acetic acid and one part of water was warmed on a steam bath until all of the solid had dissolved; this required about five minutes. The resulting light brown solution was cooled to 20—25° C. and then 8.5 ml. of 30 percent hydrogen peroxide solution (which contained 0.336 g. of hydrogen peroxide per ml. of solution) was added in one portion. The mixture became dark purple but there was no temperature rise. The reaction mixture was stirred for six hours and was then allowed to stand overnight at room temperature. A few grams of palladium-on-charcoal catalyst (10 percent palladium) was added to the reaction mixture, which was again allowed to stand overnight at room temperature. Decolorizing charcoal was added to the mixture and it was filtered. The filtrate was diluted with an equal volume of water and then chilled and filtered to remove a small amount of solid which separated from solution. To the filtrate there was gradually added 35 percent aqueous sodium hydroxide solution until the mixture was strongly alkaline. Diethyl ether was added to dissolve the liquid layer of 4-n-propylsulphinyl-3-chloroaniline which separated from the alkaline aqueous solution. The mixture was filtered to remove a small amount of insoluble material. The ethereal layer in the filtrate was separated from the aqueous layer and the latter was extracted with another portion of diethyl ether. The two ethereal extracts were combined, washed with saturated aqueous sodium chloride solution, and dried over anhydrous calcium sulphate for one hour. Decolorizing charcoal was added and the mixture was filtered. The red filtrate was distilled under reduced pressure to yield 12 g. of 4 - n - propylsulphinyl - 3 - chloroaniline as a viscous red oil. The hydrochloride is obtained by interaction of an ethereal solution of the base with one molecular equivalent of hydrogen chloride.

B. Interaction of 5.6 g. of 1,1¹ - tetramethylene - bis(3 - cyanoguanidine), 12.7 g. of 4 - n - propylsulphinyl - 3 - chloroaniline hydrochloride in 250 ml. of 2-ethoxyethanol yields the dihydrochloride of 1,1¹ - tetramethylene - bis[5 - (4 - n - propylsulphinyl-3 - chlorophenyl)biguanide] (Formula I:
R—X—=4—$CH_3CH_2CH_2$—SO—;
Y=3—Cl; Z=H; n=4).

EXAMPLE 18.

1,1¹ - Hexamethylene - bis{5 - [4 - (4-nitrophenylmercapto)phenyl]biguanide}

A. A mixture of 50.5 g. of 1,1¹ - hexamethylene-bis(3-cyanoguanidine), 115.0 g. of 4 - amino - 4¹ - nitrodiphenyl sulphide hydrochloride, and 500 ml. of 2-ethoxyethanol was refluxed for five hours. During this heating period, all of the solid dissolved and then a precipitate separated from the solution. After completion of the reflux period, the reaction mixture was filtered while hot, and the solid thus collected was purified to yield 29.1 g. of yellowish-tan powder which melted at 257—260° C. This product was the dihydrochloride of 1,1¹ - hexamethylene - bis{5 - [4 - (4 - nitrophenylmercapto)phenyl]-biguanide} (Formula I:
R—X—=4—(4—O_2N—C_6H_4)—S—;
Y=H; Z=H; n=6), having the molecular formula $C_{34}H_{38}N_{12}O_4S_2.2HCl$. The solubility of this compound at 25° C. was less than 0.25 percent, and its solubility in ethyl alcohol at 25° C. was less than 1 percent (weight/volume).

When this compound was tested for *in vitro* antibacterial and antifungal activity, the respective maximum effective aqueous dilutions showing bacteriostatic (Bs), bactericidal (Bc), fungistatic (Fs) or fungicidal (Fc) activity against the indicated test organisms were as follows: *Staphylococcus aureus* 209: Bs=1—130,000; Bc=1—40,000; *Eberthella typhi*, Hopkins: Bs=1—40,000; Bc=1—10,000. *Pseudomonas aeruginosa*: Bs=1—10,000; Bc=1—3,000. *Clostridium welchii*, M: Bs=1—130,000; Bc=1—130,000. *Mycobacterium tuberculosis*, H37Rv: Bs=1—4,000. *Tricho-*

phyton mentagrophytes: Fs = 1—10,000; Fc = 1—10,000. *Monilia albicans*: Fs = 1—10,000; Fc = 1—1,000.

EXAMPLE 19.

1,1¹ - Hexamethylene - bis{5 - [4 - (4-nitrophenylsulphonyl)phenyl]biguanide}

To a slurry of 18.0 g. of 1,1¹ - hexamethylene - bis{5 - [4 - (4 - nitrophenylmercapto)phenyl]biguanide} dihydrochloride in 75 ml. of water at 20° C. there was added dropwise 16.7 ml. (6.69 g.) of aqueous peracetic acid solution. The reaction mixture was stirred for two hours at room temperature (about 25° C.) and for two and one-half hours at 40° C. The reaction mixture was then chilled and filtered to collect the solid which had precipitated. The collected solid was washed with cold water and dried. The dry solid was ground in a mortar, washed again with cold water, re-collected, and dried. A 10 g. portion of this solid was recrystallized from 50 ml. of 50 percent aqueous acetic acid solution, using decolorizing charcoal. There was thus obtained 5 g. of white solid which melted at 220—230° C. with decomposition. This product was the dihydrochloride of 1,1¹-hexamethylene - bis{5 - [4 - (4 - nitrophenylsulphonyl)phenyl]biguanide} (Formula I: R—X— = 4—(4—O_2N—C_6H_4)—SO_2—; Y = H; Z = H; n = 6), having the molecular formula $C_{34}H_{38}N_{12}O_6S_2.2HCl$. This salt was soluble in hot N,N-dimethylformamide and in hot dimethyl sulfoxide.

EXAMPLE 20.

1,1¹ - Hexamethylene - bis{5 - [4 - (4-aminophenylmercapto)phenyl]biguanide}

To a mixture of 20 g. of the dihydrochloride hexamethylene - bis{5 - [4 - (4 - nitrophenylnitrophenylmercapto)phenyl]biguanide}, 120 ml. of 95 percent ethyl alcohol, 40 ml. of water, and 1 ml. of acetic acid, there was added in small portions, with stirring, 25 g. of iron powder (reduced with hydrogen). The reaction mixture was refluxed for six hours and was then filtered, using a steam heated filter. The filtrate was chilled for two days, and the pink solid which separated from solution was collected on a filter, washed with 75 percent aqueous ethyl alcohol solution, and dried. This solid weighed 4 g.; a 2 g. portion of it was recrystallized from 6 ml. of 50 percent aqueous acetic acid solution, using decolorizing charcoal, to yield a white solid which melted at 244—247° C. with decomposition, shrinkage beginning at 160° C. This product was the dihydrochloride of 1.1¹ - hexamethylene - bis{5 - [4 - (4 - aminophenylmercapto)phenyl]biguanide} (Formula I: R—X— = 4—(4—H_2N—C_6H_4)—S—; Y = H; Z = H; n = 6), having the molecular formula $C_{34}H_{40}N_{12}O_2S_2.2HCl$. This salt was insoluble in anhydrous ethyl alcohol and in ethyl acetate, even when these were heated. It was soluble in hot water, hot methyl alcohol, and hot 50 percent aqueous acetic acid solution.

EXAMPLE 21.

1,1¹ - Octamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide]

Following the manipulative procedure of part A of Example 1, 17.5 g. of 1,1¹ - octamethylene - bis(3 - cyanoguanidine) was interacted with 21.5 g. of 4 - methylmercaptoaniline hydrochloride in 145 ml. of 2-ethoxyethanol to produce the dihydrochloride of 1,1¹ - octamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] (Formula I: R—X— = 4—CH_3—S—; Y = H; Z = H; n = 8).

EXAMPLE 22.

1,1¹ - Decamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide]

Following the manipulative procedure of part A of Example 1 and ineracting 23.6 g. of 4 - methylmercaptoaniline hydrochloride and 23.6 g. of 1,1¹ - decamethylene - bis(3-cyanoguanidine) in 185 ml. of 2-ethoxyethanol, there was obtained the dihydrochloride of 1,1¹-decamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] (Formula I: R—X— = 4—CH_3—S—; Y = H; Z = H; n = 10).

EXAMPLE 23.

Following the same procedure as that described in part A of Example 1, but employing a mixture of 16.5 g. of 4-methylmercaptoaniline hydrochloride and 17.8 g. of 4-ethylmercaptoaniline hydrochloride instead of the 4-methylmercaptoaniline hydrochloride alone, there is produced a mixture of the dihydrochlorides of the symmetrical compounds 1,1¹-hexamethylene - bis[5 - (4 - methylmercaptophenyl)biguanide] and 1,1¹ - hexamethylene-bis[5 - (4 - ethylmercaptophenyl)biguanide] and of the unsymmetrical compound 1 - (4-methylmercaptophenylbiganido) - 6 - (4-ethylmercaptophenylbiguanido)hexane. It is not necessary to separate this mixture into its several constituents, although this can be done, if desired, by conventional crystallization procedures, since the mixture is directly useful as an antibacterial, antifungal, and antiviral agent. By treating the mixture of dihydrochlorides with sodium hydroxide, there is obtained a mixture of the corresponding free organic bases, which interacts with acids to form a mixture of the respective acid-addition salts of the bases.

The following compounds, and acid-addition salts thereof, can be obtained by using procedures similar to those described above:

1,1¹ - hexamethylene - bis[5 - (2 - methylmercaptophenyl)biguanide]

1,1¹ - hexamethylene - bis[5 - (3 - methylmercaptophenyl)biguanide]

1,1¹ - hexamethylene - bis[5 - (4 - methylsulphinylphenyl)biguanide]
1,1¹ - pentamethylene - bis[5 - (2 - methylmercaptophenyl)biguanide]
1,1¹ - heptamethylene - bis[5 - (3 - methylmercaptophenyl)biguanide]
1,1¹ - ethylene - bis[5 - (4 - methylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (3 - ethylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (4 - ethylsulphinylphenyl)biguanide]
1.1¹ - hexamethylene - bis[5 - (3 - ethylsulphonylphenyl)biguanide]
1,1¹ - decamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide]
1,1¹ - dodecamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide]
1,1¹ - dodecamethylene - bis[5 - (4 - ethylsulphonylphenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (4 - n-hexylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (4 - n - octadecylmercaptophenyl)biguanide]
1,1¹ - pentamethylene - bis[5 - (4 - methylmercapto - 3 - fluorophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (2 - methylmercapto - 5 - chlorophenyl)biguanide]
1,1¹ - tetramethylene - bis[5 - (4 - n-propylsulphonyl - 3 - chlorophenyl)biguanide]
1,1¹ - trimethylene - bis[5 - (4 - n - hexylmercapto - 3 - chlorophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (4 - methylmercapto - 3 - trifluoromethylphenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (5 - methylmercapto - 2 - nitrophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (2 - methylmercapto - 4 - methoxyphenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (4 - ethylmercapto - 2 - methylphenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (4 - n - butylsulphonyl - 2,5 - dimethoxyphenyl)biguanide]
1,1¹ - hexamethylene - bis{5 - [2,4 - bis(methylmercapto)phenyl]biguanide}
1,1¹ - hexamethylene - bis{5 - [2 - bromo-4,6 - bis(methylsulphonyl)phenyl]biguanide}
1,1¹ - hexamethylene - bis[5 - (3 - trifluoromethylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (6 - trifluoromethylsulphonyl - 2,4 - dinitrophenyl)biguanide]
1,1¹ - octamethylene - bis[5 - (2 - allylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (4 - cyclohexylmercaptophenyl)biguanide]
1,1¹ - decamethylene - bis[5 - (4 - phenylmercaptophenyl)biguanide]
1,1¹ - decamethylene - bis[5 - (4 - phenylsulphinylphenyl)biguanide]
1.1¹ - hexamethylene - bis{5 - [4 - (4-nitrophenylsulphinyl)phenyl]biguanide}
1,1¹ - (1,5 - hexylene)bis[5 - (4 - methylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis{5 - [4 - (4-iodophenylmercapto)phenyl]biguanide}
1,1¹ - hexamethylene - bis{5 - [4 - (4 - aminobenzylmercapto)phenyl]biguanide}
1,1¹ - hexamethylene - bis[5 - (2 - benzylsulphonyl - 4 - ethylsulphonylphenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (2 - methylsulphonyl - 4 - ethylsulphonylphenyl)biguanide]
1,1¹ - octamethylene - bis[5 - (4 - methallylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis[5 - (3 - benzylmercaptophenyl)biguanide]
1,1¹ - hexamethylene - bis{5 - [4 - (benzylsulphinyl)phenyl]biguanide}
1,1¹ - hexamethylene - bis{5 - [2 - (3,4-dichlorobenzyl)sulphonylphenyl]biguanide}
1,1¹ - hexamethylene - bis{5 - [2 - (4-methylbenzylsulphonyl) - 5 - chlorophenyl]-biguanide}
1,1¹ - hexamethylene - bis{5 - [4 - (4-methoxybenzylsulphonylphenyl]biguanide}
1,1¹ - hexamethylene - bis{5 - [4 - (4-nitrobenzylmercapto)phenyl]biguanide}
1.1¹ - heptamethylene - bis{5 - [4 - (4-methylphenylmercapto)phenyl]biguanide}
1,1¹ - pentamethylene - bis{5 - [4 - (4-methoxyphenylmercapto)phenyl]biguanide}
1,1 - heptamethylene - bis{5 - [(4 - methylphenylsulphinyl)phenyl]biguanide}
1,1¹ - pentamethylene - bis{5 - [4 - (4-methoxyphenylsulphinyl)phenyl]biguanide}
1,1¹ - heptamethylene - bis{5 - [4 - (4-methylphenylsulphonyl)phenyl]biguanide}
1,1¹ - pentamethylene - bis{5 - [4 - (4-methoxyphenylsulphonyl)phenyl]biguanide}, and
1,1¹ - (1,4 - pentylene)bis[5 - (4 - methylmercaptophenyl)biguanide].

WHAT WE CLAIM IS:—

1. A compound having the general formula I (herein) wherein C_nH_{2n} represents a bivalent alkylene bridge in which the free valence bonds are on two different carbon atoms and n is an integer from 2 to 12 inclusive and Q and Q¹ each represent substituted phenyl having the structural formula Ia (herein) wherein Y is hydrogen, halogen, trifluoromethyl, nitro, C_1 to C_6 alkyl—O, C_1 to C_6 alkyl—S—, C_1 to C_6 alkyl—SO—, or C_1 to C_6 alkyl—SO_2—; Z is hydrogen, halogen, nitro, C_1 to C_6 alkyl, or C_1 to C_6 alkyl—O—; R is alkyl, halo—C_1 to C_6 alkyl, C_2 to C_6 alkenyl, benzyl, *ar*-halobenzyl, *ar*-nitrobenzyl, *ar*-C_1 to C_6 alkylbenzyl, *ar*—C_1 to C_6 alkoxybenzyl, cyclohexyl, phenyl, C_1 to C_6 alkylphenyl, nitrophenyl, C_1 to C_6 alkoxyphenyl, halophenyl, or when neither Y nor Z is nitro, *ar*-aminobenzyl or aminophenyl; and X is —S—, —SO—, or —SO_2—; or an acid-addition salt thereof.

2. A compound according to claim 1, wherein Q and/or Q¹ represent(s) alkylmercapto-

phenyl, alkylsulphinylphenyl, alkylsulphonylphenyl, or alkylmercaptohalophenyl.

3. A compound according to claim 2, wherein Q and/or Q^1 represent(s) 4—C_1 to C_6—alkylmercaptophenyl, 4—C_1 to C_6—alkylsulphonylphenyl, or 4—C_1 to C_6—alkylmercapto-3-halophenyl.

4. A compound according to any one of the preceding claims, wherein n is from 5 to 7 inclusive.

5. $1,1^1$ - Hexamethylene - bis[5 - (4-methylmercaptophenyl)biguanide].

6. $1,1^1$ - Hexamethylene - bis[5 - (4 - ethylmercaptophenyl)biguanide].

7. $1,1^1$ - Hexamethylene - bis[5 - (4 - n-butylmercaptophenyl)biguanide].

8. $1,1^1$ - Hexamethylene - bis[5 - (3 - n-amylmercaptophenyl)biguanide].

9. $1,1^1$ - Hexamethylene - bis[5 - (4-methylmercapto - 3 - chlorophenyl)biguanide].

10. $1,1^1$ - Hexamethylene - bis[5 - (4-ethylmercapto - 3 - chlorophenyl)biguanide].

11. $1,1^1$ - Hexamethylene - bis[5 - (4 - n-propylmercapto - 3 - chlorophenyl)biguanide].

12. A compound according to claim 1 as herein described.

13. A process for preparing $1,1^1$- (alkylene)-bis(5 - arylbiguanides or acid-addition salts thereof which comprises interacting a $1,1^1$-(alkylene) bis(3-cyanoguanidine) having the general formula II (herein) wherein C_nH_{2n} represents a bivalent alkylene bridge in which the free valence bonds are on two different carbon atoms and n is 2 to 12, with approximately two molecular proportions of an arylamine, preferably as its acid-addition salt, having the general formula III (herein) wherein Y is hydrogen, halogen, trifluoromethyl, nitro, C_1 to C_6 alkyl—O—, C_1 to C_6 alkyl—S—, C_1 to C_6 alkyl—SO—, or C_1 to C_6 alkyl—SO_2—; Z is hydrogen, halogen, nitro, C_1 to C_6 alkyl, or C_1 to C_6 alkyl—O—; R^1 is alkyl, halo—C_1 to C_6 alkyl, C_2 to C_6 alkenyl, benzyl, *ar*-halobenzyl, *ar*-nitrobenzyl, *ar*-C_1 to C_6 alkylbenzyl, *ar*-C_1 to C_6 alkoxybenzyl, cyclohexyl, phenyl, C_1 to C_6 alkylphenyl, nitrophenyl, C_1 to C_6 alkoxyphenyl, or halophenyl; and X is —S—, —SO—, or —SO_2—; or interacting an alkylenediamine, as its acid-addition salt, having the general formula (IV) herein with approximately two molecular proportions of a 1-aryl-3-cyanoguanidine having the structural formula (V) herein; if desired, reducing the compound obtained wherein R^1 is *ar*-nitrobenzyl or nitrophenyl and wherein neither Y nor Z is nitro to obtain the corresponding *ar*-aminobenzyl or aminophenyl compound; if desired, oxidizing the compound obtained wherein X is —S— to the corresponding compound wherein X is —SO— or —SO_2—; and, if desired, obtaining an acid-addition salt of any free base obtained or neutralizing an acid-addition salt obtained to form the free base.

14. A process according to claim 13 which comprises interacting $1,1^1$ - hexamethylene-bis(3-cyanoguanidine) with approximately two molecular proportions of a C_1 to C_6 alkylmercaptoaniline hydrochloride.

15. A process according to claim 13 which comprises interacting $1,1^1$ - hexamethylene-bis(3 - cyanoguanidine) with approximately two molecular proportions of a C_1 to C_6 alkylmercapto-haloaniline hydrochloride.

16. A process according to claim 13 which comprises interacting $1,1^1$ - hexamethylene-diamine dihydrochloride with approximately two molecular proportions of a 1-aryl-3-cyanoguanidine having the formula V (herein) wherein Y and Z are hydrogen and R^1—X is C_1 to C_6 alkyl-mercapto.

17. A process for preparing $1,1^1$ - (alkylene)-bis-(5-aryl-biguanides) or acid-addition salts thereof as claimed in claim 1, substantially as herein described with reference to the Examples.

18. A compound prepared by the process according to any one of claims 13 to 17.

19. A disinfecting or sanitizing composition which comprises a compound according to any one of claims 1 to 12 and 18 and a suitable carrier.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1964. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.